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Enfortumab Vedotin With or Without Pembrolizumab in Cisplatin-Ineligible Patients With Previously Untreated Locally Advanced or Metastatic Urothelial Cancer

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ABSTRACT

PURPOSE Patients with locally advanced or metastatic urothelial cancer (la/mUC) who are ineligible for cisplatin-based therapy have limited first-line (1L) treatment options and significant need for improved therapies. Enfortumab vedotin (EV) and pembrolizumab (Pembro) individually have shown a survival benefit in urothelial cancer in second-line + la/mUC settings. Here, we present data from the pivotal trial of EV plus Pembro (EV + Pembro) in the 1L setting.

PATIENTS AND METHODS In Cohort K of the EV-103 phase Ib/II study, cisplatin-ineligible patients with previously untreated la/mUC were randomly assigned 1:1 to receive EV as monotherapy or in combination with Pembro. The primary end point was confirmed objective response rate (cORR) per blinded independent central review. Secondary end points included duration of response (DOR) and safety. There were no formal statistical comparisons between treatment arms.

RESULTS The cORR was 64.5% (95% CI, 52.7 to 75.1) and 45.2% (95% CI, 33.5 to 57.3) for patients treated with EV + Pembro (N = 76) and EV monotherapy (N = 73), respectively. The median DOR was not reached for the combination and was 13.2 months for monotherapy; 65.4% and 56.3% of patients who responded to the combination and monotherapy, respectively, maintained a response at 12 months. The most common grade 3 or higher treatment-related adverse events (TRAEs) in patients treated with the combination were maculopapular rash (17.1%), fatigue (9.2%), and neutropenia (9.2%). EV TRAEs of special interest (any grade) in the combination arm included skin reactions (67.1%) and peripheral neuropathy (60.5%).

CONCLUSION EV + Pembro showed a high cORR with durable responses as 1L treatment in cisplatin-ineligible patients with la/mUC. Patients who received EV monotherapy had a response and safety profile consistent with previous studies. Adverse events for EV + Pembro were manageable, with no new safety signals observed.

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INTRODUCTION

The occurrence of urothelial cancer is increasing worldwide, with locally advanced or metastatic urothelial cancer (la/mUC) demonstrating an especially poor prognosis.[1-4] Cisplatin-based chemotherapy is the gold standard first-line (1L) treatment in patients with la/mUC, but approximately half of all patients are ineligible for 1L cisplatin-based chemotherapy because of impaired renal function, poor performance status, and other comorbidities.[5-8] Carboplatin plus gemcitabine is a commonly used regimen for cisplatin-ineligible patients but has shown lower activity and poor tolerability.[9-12] Other therapeutic options exist but are limited to subgroups of patients; avelumab maintenance therapy is approved for patients who have remained free from disease progression after 1L platinum-based treatment and has shown improved survival; however, only patients who do not progress after four to six cycles of 1L therapy are eligible.[13,14] Single-agent PD-1/PD-L1 checkpoint inhibitors (CPIs) may be another 1L option for cisplatin-ineligible patients; however,

CONTEXT

Key Objective

To assess the efficacy, tolerability, and safety of enfortumab vedotin (EV) in combination with pembrolizumab (Pembro) in cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial cancer.

Knowledge Generated

EV + Pembro showed a high confirmed objective response rate of 64.5%, and rapid and durable responses, with 65.4% of responders maintaining a response at 12 months (Kaplan-Meier estimate). The combination demonstrated a manageable safety profile.

Relevance *(M.A. Carducci)*

This report provides a strong foundation for the ongoing phase III studies of the EV and Pembro combination in muscle invasive bladder cancer. Toxicities although manageable are increased over EV alone and maturation of the survival data may also shed light on addressing toxicity, both clinical and financial, concerns as well as sequencing approaches.*

*Relevance section written by *JCO* Associate Editor Michael A. Carducci, MD.

they have become increasingly restricted to certain populations. In the United States currently, pembrolizumab (Pembro) is limited to 1L patients who are not eligible for any platinum-based chemotherapy.[15-19] Additionally, approximately 60% of cisplatin-ineligible patients with la/mUC who receive 1L treatment do not receive second-line (2L) treatment.[20] This underscores the need for efficacious and tolerable 1L therapies.

Enfortumab vedotin (EV), an antibody-drug conjugate (ADC), comprises a fully human monoclonal antibody specific for nectin-4 and monomethyl auristatin E (MMAE). EV delivers MMAE to cells expressing nectin-4, leading to cell cycle arrest and cell death. Pembro is an anti–PD-1 antibody that uses the PD-1 receptor as a therapeutic target and has antitumor activity in multiple tumor types.[16]

EV and Pembro as individual agents have shown overall survival (OS) benefits compared with 2L or third-line treatment in patients with la/mUC.[16,21,22] Preclinical data have shown that vedotin ADCs, including EV, in combination with PD-1/PD-L1 inhibitors such as Pembro, may enhance antitumor activity relative to their respective mechanisms of action and support complimentary efficacy.[23-25]

In the phase Ib/II study EV-103, results from the Dose Escalation/Cohort A demonstrated high antitumor activity and durable responses with encouraging survival and a manageable safety profile for EV plus Pembro (EV + Pembro), providing the rationale for further evaluation.[26] Randomized Cohort K is intended to provide efficacy and safety data on the treatment combination. The EV monotherapy arm was included to better understand the safety and efficacy of EV monotherapy in 1L cisplatin-ineligible patients. No statistical comparison between treatment arms was performed.

Here, we present the efficacy and safety results of EV-103 randomized Cohort K for cisplatin-ineligible patients with la/mUC treated with EV + Pembro or EV monotherapy in the 1L setting.

PATIENTS AND METHODS

Trial Participants

In Cohort K of the EV-103 study, eligible patients were 18 years or older with histologically documented la/mUC, including squamous differentiation or mixed cell types. Patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or less and were eligible for Pembro therapy. Patients in Cohort K were deemed ineligible for cisplatin-based chemotherapy on the basis of at least one of the following: glomerular filtration rate (GFR) <60 mL/min and ≥30 mL/min, grade ≥ 2 hearing loss, ECOG PS of 2, or New York Heart Association (NYHA) Class III heart failure. Patients with an ECOG PS of 2 met additional criteria: hemoglobin ≥ 10 g/dL, GFR ≥ 50 mL/min, and no NYHA Class III heart failure. Patients were excluded from the trial if they had any of the following: previous systemic treatment for locally advanced or metastatic disease, including adjuvant/neoadjuvant platinum-based therapy within 12 months before random assignment, previous treatment with a PD-1, PD-L1, or PD-L2 inhibitor, or any previous treatment with stimulatory or coinhibitory T-cell receptor agents, previous treatment with EV or another MMAE-based ADC, ongoing grade 2 or higher sensory or motor neuropathy, or ongoing clinically significant toxic effects associated with previous treatment, active central nervous system metastases, or uncontrolled diabetes (defined as hemoglobin A1c [HbA1c] ≥ 8% or HbA1c 7% to <8% with associated diabetes symptoms [polyuria or polydipsia] that were not otherwise explained). Full eligibility criteria are provided in the study Protocol (online only).

Random Assignment and Treatment

Enrolled patients were randomly assigned 1:1 to receive EV alone or in combination with Pembro. Random assignment was stratified by ECOG PS (0 *v* 1 or 2) and liver metastasis (present *v* absent) at baseline. EV was administered at a dose of 1.25 mg per kilogram of body weight (maximum total dose of 125 mg) as a single intravenous infusion over 30 minutes on days 1 and 8 of a 3-week cycle. Pembro was administered at a dose of 200 mg as a single intravenous infusion over 30 minutes on day 1 of a 3-week cycle. Dose modifications and reductions were permitted to manage treatment-related adverse events (TRAEs) as described in the study Protocol.

Trial Oversight

The study was designed by the sponsors in collaboration with an advisory committee. The trial received approval from site independent institutional review boards or ethics committees and was conducted in accordance with the ethics principles of the Declaration of Helsinki and with Good Clinical Practice guidelines defined by the International Council for Harmonization. All patients provided written informed consent. The trial was sponsored by Seagen Inc (Bothell, WA), Astellas Pharma (Northbrook, IL), and Merck Sharp & Dohme LLC (Rahway, NJ). The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the Protocol.

End Points

The primary end point was confirmed objective response rate (cORR; proportion of patients with a complete or partial response) per RECIST version 1.1 by blinded independent central review (BICR). Secondary end points were cORR by investigator, disease control rate (DCR) by BICR and investigator assessment, duration of response (DOR) and progression-free survival (PFS) by BICR and investigator assessment, OS, and safety and tolerability of EV monotherapy and EV + Pembro. Exploratory end points included biomarkers of activity, including baseline PD-L1 status and nectin-4 expression.

Assessments

Investigators assessed and confirmed antitumor activity by reviewing computed tomography scans or magnetic resonance imaging with or without intravenous contrast of the chest, abdomen, and pelvis. Patients were evaluated for response assessments using the same imaging method throughout the study. Bone and brain scans were required at screening and repeated if positive at baseline and/or if clinically indicated. Objective responses were confirmed per RECIST version 1.1, with repeat scans 4-5 weeks after a first documented response. Subsequent response assessments were timed from cycle 1 day 1 and were performed every 9 weeks (±7 days) until 1 year after the first dose and then every 12 weeks (±7 days).

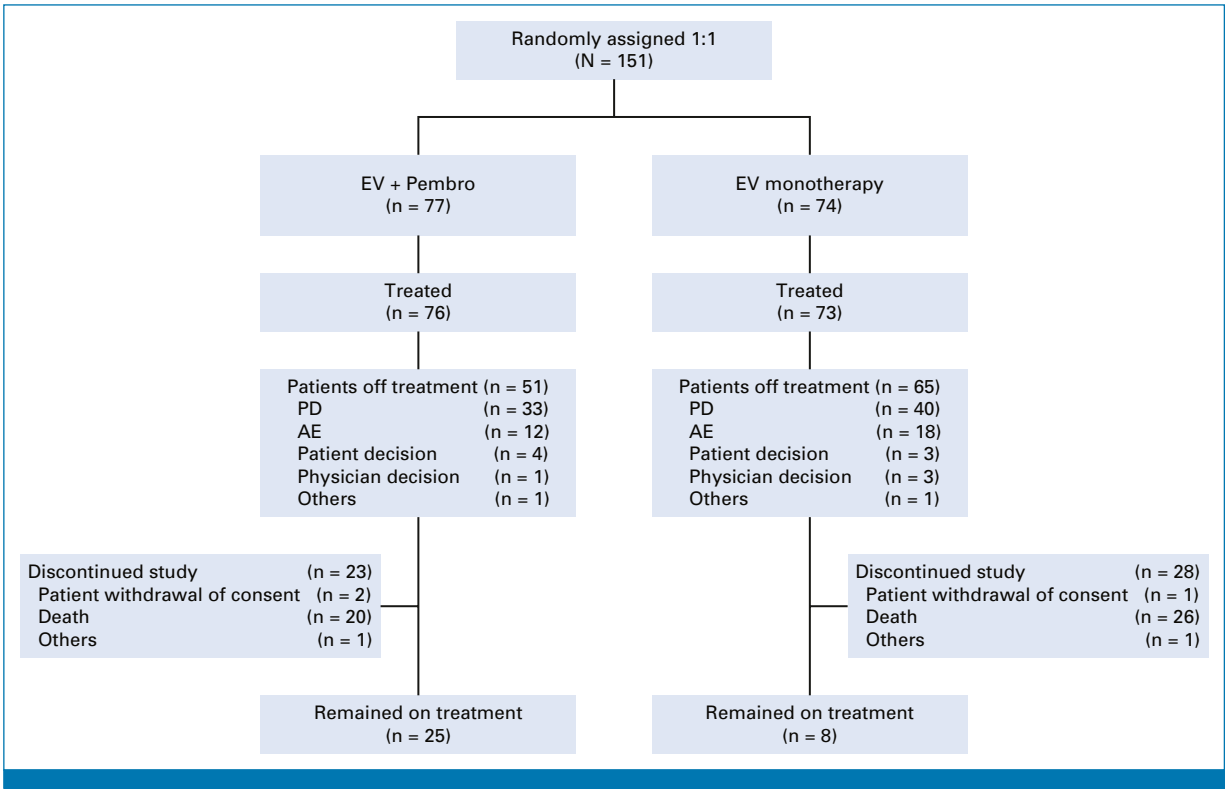

FIG 1. CONSORT diagram. Screening, allocation, follow-up, and analyses. A patient is considered discontinued from the treatment only if both agents are discontinued, including patients who discontinued both agents because of AE(s) or discontinued the latter of the two agents because of an AE (the other agent may be discontinued because of a non-AE at an earlier time). AE, adverse event; EV, enfortumab vedotin; PD, progressive disease; Pembro, pembrolizumab.

TABLE 1. Patient Demographics and Disease Characteristics at Baseline

Characteristic	EV + Pembro (N = 76)	EV monotherapy (N = 73)
Sex, male, No. (%)	54 (71.1)	56 (76.7)
Age, years, median (range)	71 (51-91)	74 (56-89)
Race, White, No. (%)	61 (80.3)	55 (75.3)
ECOG PS, No. (%)		
0	33 (43.4)	28 (38.4)
1	33 (43.4)	35 (47.9)
2	10 (13.2)	10 (13.7)
Primary tumor location,[a] No. (%)		
Lower tract	46 (60.5)	51 (69.9)
Upper tract	30 (39.5)	21 (28.8)
Metastasis disease sites,[b] No. (%)		
Bone	19 (25.0)	21 (28.8)
Liver	13 (17.1)	13 (17.8)
Lung	37 (48.7)	30 (41.1)
Metastasis category, No. (%)		
Lymph node only	10 (13.2)	12 (16.4)
Visceral disease	64 (84.2)	60 (82.2)
Not applicable[c]	2 (2.6)	1 (1.4)
PD-L1 status by CPS, No. (%)		
CPS < 10	44 (57.9)	38 (52.1)
CPS ≥ 10	31 (40.8)	28 (38.4)
Not evaluable	1 (1.3)	7 (9.6)

Abbreviations: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; Pembro, pembrolizumab.

[a]One patient in the EV monotherapy arm had primary disease at both the bladder and uterer.

[b]Excludes sites other than bone, liver, and lung. Patients may have metastatic disease in more than one location.

[c]Patients had locally advanced disease without metastasis to lymph nodes or distant organs.

EV adverse events of special interest (AESIs) are medical concepts/composite terms used to characterize identified and potential risks for EV. AESI time-to-onset is calculated as time from the date of the first dose to the start date of the first treatment emergent event that meets the respective AESI search criteria. TRAEs were determined by the investigator and assessed for both arms. Pembro AESIs (AEOSIs), including immune-mediated adverse events (AEs) and infusion reactions, were evaluated using previously described criteria for Pembro monotherapy.[16]

Treatment discontinuations were summarized according to the percentage of patients who had TRAEs leading to discontinuation of either agent, including patients who had TRAEs leading to discontinuation of EV only, Pembro only, or both. Of note, discontinuations because of each agent alone, or both, are counted by patient and are not mutually exclusive.

Nectin-4 and PD-L1 expression were assessed centrally with archival or freshly obtained formalin-fixed, paraffin-embedded tumor tissue using analytically validated immunohistochemistry (IHC) assays. Nectin-4 expression was evaluated at Q2 Solutions as described previously, and stained slides were scored by a pathologist to generate an H-score (range, 0-300).[27] PD-L1 expression was assessed using the Agilent PD-L1 IHC 22C3 pharmDx assay, with stained slides scored by a pathologist to generate a PD-L1 combined positive score (CPS; low, <10; high, ≥10).

Statistical Analysis

Efficacy and safety end points were assessed for all patients who received EV + Pembro or EV monotherapy. The sample size was based on the precision of the estimate for objective response rate (ORR) as characterized by 95% CIs. The cORR by BICR was summarized with two-sided 95% CI and calculated using the Clopper-Pearson method for each treatment arm. No statistical comparisons were made between treatment arms; EV monotherapy arm was included for isolation of the monotherapy contribution. Secondary end points, cORR by investigator assessment and DCR by BICR and investigator assessment, were summarized with two-sided 95% CIs using the Clopper-Pearson method. DOR and PFS by BICR and by investigator assessment and OS were analyzed using Kaplan-Meier methodology. ORR, DOR, and PFS are presented by BICR in results.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 151 patients were randomly assigned and 149 received EV + Pembro (N = 76) or EV monotherapy (N = 73; Appendix Table A1, online only). Two patients, one in each arm, were randomly assigned but never received corresponding study treatment (Fig 1). At data cutoff (June 10, 2022), 29 patients in the combination arm had discontinued treatment but remained in the study in long-term follow-up. The median follow-up on study was 14.8 months (95% CI, 12.9 to 17.3) in the combination arm and 15.0 months (95% CI, 12.7 to 17.4) in the monotherapy arm. The median duration of treatment was 9.0 months (range, 0.6-26.1) in the combination arm with patients receiving a median of 11.0 cycles (range, 1-29). The median duration of treatment was 5.5 months (range, 0.5-26.9) in the monotherapy arm with patients receiving a median of 8.0 cycles (range, 1-33).

In the combination arm, patients were predominately male (71.1%) and White (80.3%), with a median age of 71 years (range, 51-91 years). Most patients had an ECOG PS of 0 (43.4%) or 1 (43.4%). The primary disease location was the lower tract (60.5%). Visceral metastases were present in 84.2% of patients, including 17.1% with liver metastases. At baseline, 57.9% of patients had low PD-L1 expression (defined as CPS < 10) (Table 1). The median nectin-4 H-score

A

	EV + Pembro (N = 76)	EV Monotherapy (N = 73)
Confirmed ORR, No. (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response		
CR	8 (10.5)	3 (4.1)
PR	41 (53.9)	30 (41.1)
Stable disease	17 (22.4)	25 (34.2)
PD	6 (7.9)	7 (9.6)
Not evaluable	3 (3.9)	5 (6.8)
No assessment	1 (1.3)	3 (4.1)
Time to objective response, months, median (range)	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Treatment cycles, No., months, median (range)	11.0 (1, 29)	8.0 (1, 33)

B

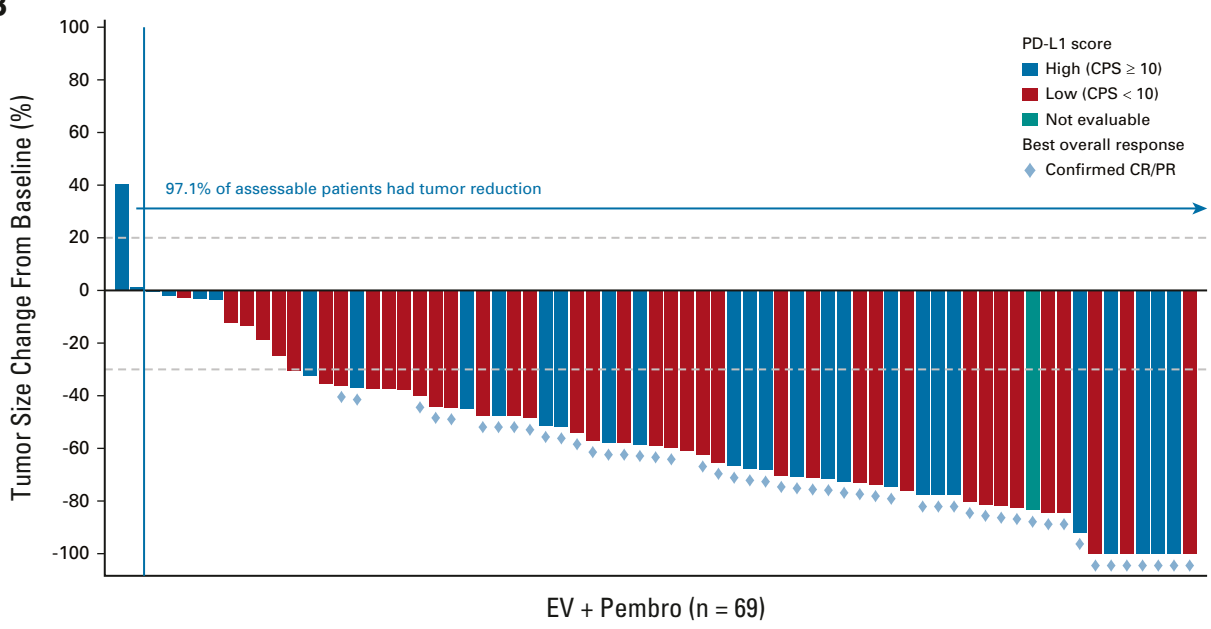

FIG 2. (A) Best overall response by BICR. (B) Antitumor activity of EV + Pembro, waterfall plot of percentage reduction of tumor size from baseline of target lesions by BICR per RECIST v1.1. BICR, blinded independent central review; CPS, combined positive score; CR, complete response; EV, enfortumab vedotin; ORR, objective response rate; PD, progressive disease; Pembro, pembrolizumab; PR, partial response.

at baseline was 262.5 (interquartile range [IQR], 200.0-297.0).

Baseline characteristics of patients in the monotherapy arm are summarized in Table 1. The median H-score at baseline was 284.0 (IQR, 240.0-298.0).

Efficacy

In patients treated with EV + Pembro (N = 76), the cORR by BICR was 64.5% (95% CI, 52.7 to 75.1; 49 of 76 patients). Eight patients (10.5%) had a complete response; 41 patients (53.9%) achieved a partial response; the median time to response was 2.1 months (range, 1.1-6.6; Fig 2). A total of 97.1% of assessable patients had a reduction in their target lesions per BICR (Fig 2). The median DOR per BICR has not yet been reached; 65.4% of responders maintained a response at 12 months (Fig 3). The DCR was 86.8% (95% CI, 77.1 to 93.5; 66 of 76 patients). The PFS rate per BICR at 6 and 12 months was 73.8% and 55.1%, respectively, and the OS rate at 6 and 12 months was 88.2% and 80.7%, respectively (Fig 4). The median OS was 22.3 months (95% CI, 19.09 to not achieved) with 54 (of 76) patients remaining on study for OS follow-up at the time of data cutoff (Appendix Fig A1, online only).

A

	EV + Pembro (N = 76)	EV Monotherapy (N = 73)
Responders, No.	49	33
Progression events, No.	13	14
DOR ≥ 12 months,%	65.4	56.3
mDOR, months 95% CI	– (10.25, –)	13.2 (6.14, 15.97)

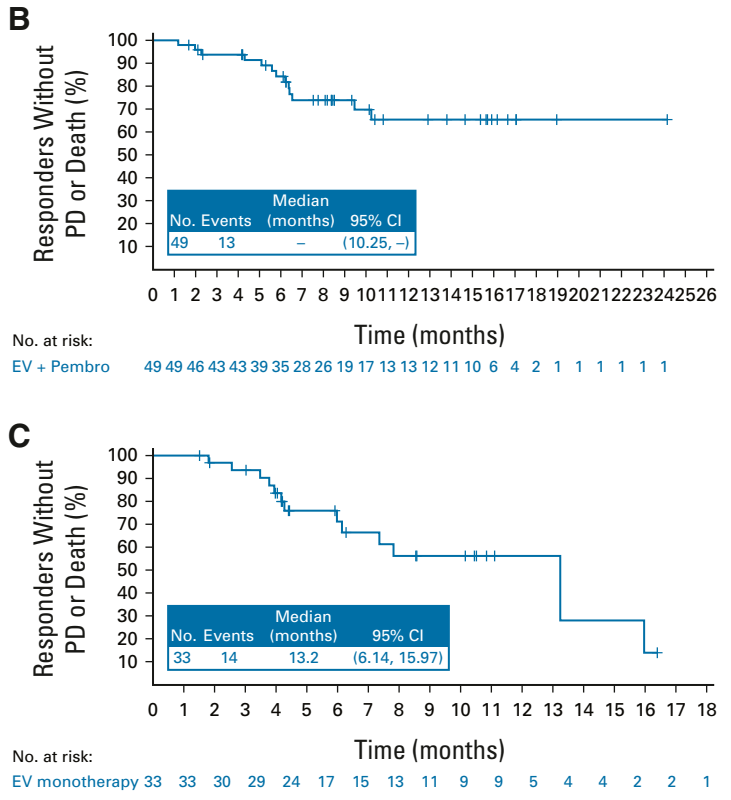

FIG 3. (A) Durations of response per BICR by RECIST v1.1. (B) Kaplan-Meier estimate of durations of response per BICR, EV + Pembro treatment arm. (C) Kaplan-Meier estimate of durations of response per BICR, EV monotherapy treatment arm. This study was not designed with statistical comparison between the two treatment arms; direct comparisons should not be made. BICR, blinded independent central review; DOR, duration of response; EV, enfortumab vedotin; mDOR, median duration of response; mono, monotherapy; PD, progressive disease; Pembro, pembrolizumab; v1.1, version 1.1.

The cORR in prespecified subgroups in the combination arm (including PD-L1 expression, liver metastasis, ECOG PS, and primary disease site of origin) was consistent with overall cORR (Appendix Fig A2, online only).

Nectin-4 expression was generally high as indicated by median H-score in the combination arm, and the distribution was similar between responders (median, 260.0; IQR, 200.0-297.0) and nonresponders (270.0; 155.0-300.0; Appendix Fig A3, online only).

In the monotherapy arm, the cORR per BICR was 45.2% (95% CI, 33.5 to 57.3; 33 of 73 patients; Fig 2). The DOR was 13.2 months (range, 6.14-15.97), and the median time to response was 2.1 months (range, 1.9-15.4). The DCR was 79.5% (95% CI, 68.4 to 88.0; 58 of 73 patients). The 12-month PFS and OS were 35.8% and 70.7%, respectively (Fig 5). The cORR per BICR for prespecified subgroups can be found in Appendix Figure A2. The nectin-4 H-score median and distribution were similar between responders and nonresponders (Appendix Fig A3).

The concordance rate of best overall response per RECIST between BICR and investigator assessments was 86.7% in the combination arm and 85.5% in the monotherapy arm.

Safety

In patients treated with the combination, the most common TRAEs were fatigue, peripheral sensory neuropathy, alopecia, and maculopapular rash; the most common grade 3 or higher event was maculopapular rash (Table 2). Eighteen (23.7%) patients experienced a serious TRAE, and three (3.9%) patients died due to a TRAE (respiratory failure, pneumonitis, and sepsis). TRAEs leading to dose interruptions of either EV or Pembro occurred in 68.4% of patients. TRAEs leading to discontinuation of EV and/or Pembro are listed in Table 2. The most frequently occurring TRAEs leading to discontinuation of either agent was peripheral neuropathy (nine of 76 patients, 11.8%) and of EV only was peripheral neuropathy (nine of 76 patients, 11.8%) and Pembro only was pneumonitis (three of 76 patients, 3.9%). TRAEs leading to discontinuation of both agents were

A

	EV + Pembro (N = 76)
PFS events, No.	31
PFS rate at 12 months, % 95% CI	55.1 (41.84, 66.48)
mPFS, months 95% CI	– (8.31, –)
OS events, No.	20
OS rate at 12 months, % 95% CI	80.7 (69.42, 88.13)
mOS, months 95% CI	22.3 (19.09, –)
Follow-up time, months, median 95% CI	14.8 (12.91, 17.28)

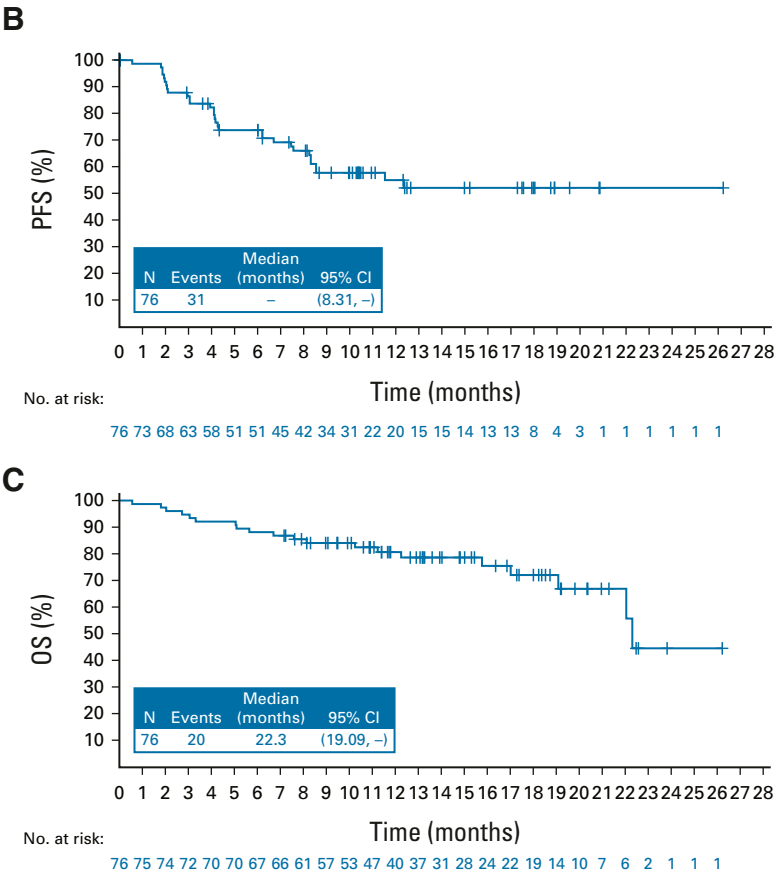

FIG 4. EV + Pembro. (A) PFS per BICR, by RECIST v1.1, OS, and median follow-up time. (B) Kaplan-Meier estimate of PFS per BICR by RECIST v1.1. (C) Kaplan-Meier estimate of OS. Preliminary mPFS and mOS are reported here and are expected to evolve over time. At the time of data cutoff, 54 (of 76) patients remain on study for OS follow-up. BICR, blinded independent central review; EV, enfortumab vedotin; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; Pembro, pembrolizumab; PFS, progression-free survival; v1.1, version 1.1.

peripheral motor neuropathy, myasthenia gravis, pneumonitis, and sepsis (one patient [1.3%] each).

Treatment-related EV AESIs in the combination arm were peripheral neuropathy (46 of 76 patients, 60.5%), skin reactions (51 of 76 patients, 67.1%), hyperglycemia (11 of 76 patients, 14.5%), ocular events (20 of 76 patients, 26.3%), and infusion-related reactions (three of 76 patients, 3.9%; Appendix Table A2, online only). Grade 3 or higher skin reactions, peripheral neuropathy, and hyperglycemia in the combination arm occurred in 16 of 76 (21.1%), two of 76 (2.6%), and five of 76 (6.6%) patients, respectively. No serious skin reactions occurred, including no severe cutaneous adverse reaction events. One patient experienced serious peripheral neuropathy (1.3%).

The most frequent Pembro treatment-emergent AEOSIs in the combination arm were severe skin reactions (21 of 76 patients, 27.6%) and hypothyroidism (10 of 76 patients, 13.2%); the most common grade 3 or higher AEOSIs were severe skin reactions (15 of 76 patients, 19.7%) and pneumonitis (four of 76 patients, 5.3%; Appendix Table A3, online only). Pembro AEOSIs associated with the use of systemic steroids are reported in the Protocol.

TRAEs and deaths in patients treated with monotherapy are summarized in Table 2. The most frequent treatment-related EV AESIs reported in patients in the monotherapy arm were peripheral neuropathy and skin reactions (Appendix Table A2).

DISCUSSION

Approximately half of all patients with la/mUC are unfit for 1L cisplatin-based chemotherapy, and limited 1L therapeutic options exist for these patients.[20,28] Carboplatin plus gemcitabine is currently a standard option for cisplatin-ineligible patients but is associated with low response rate (approximately 36%-42%), short DOR (6.3-7.1 months), and relatively poor tolerability.[9,29,30] In this study of cisplatin-ineligible patients with la/mUC, EV in combination with Pembro showed a 64.5% overall response rate, with responses lasting beyond 1 year for 65.4% of responders, trending similarly with previously disclosed data from EV-103 Dose Escalation/Cohort A.[26] Additionally, the

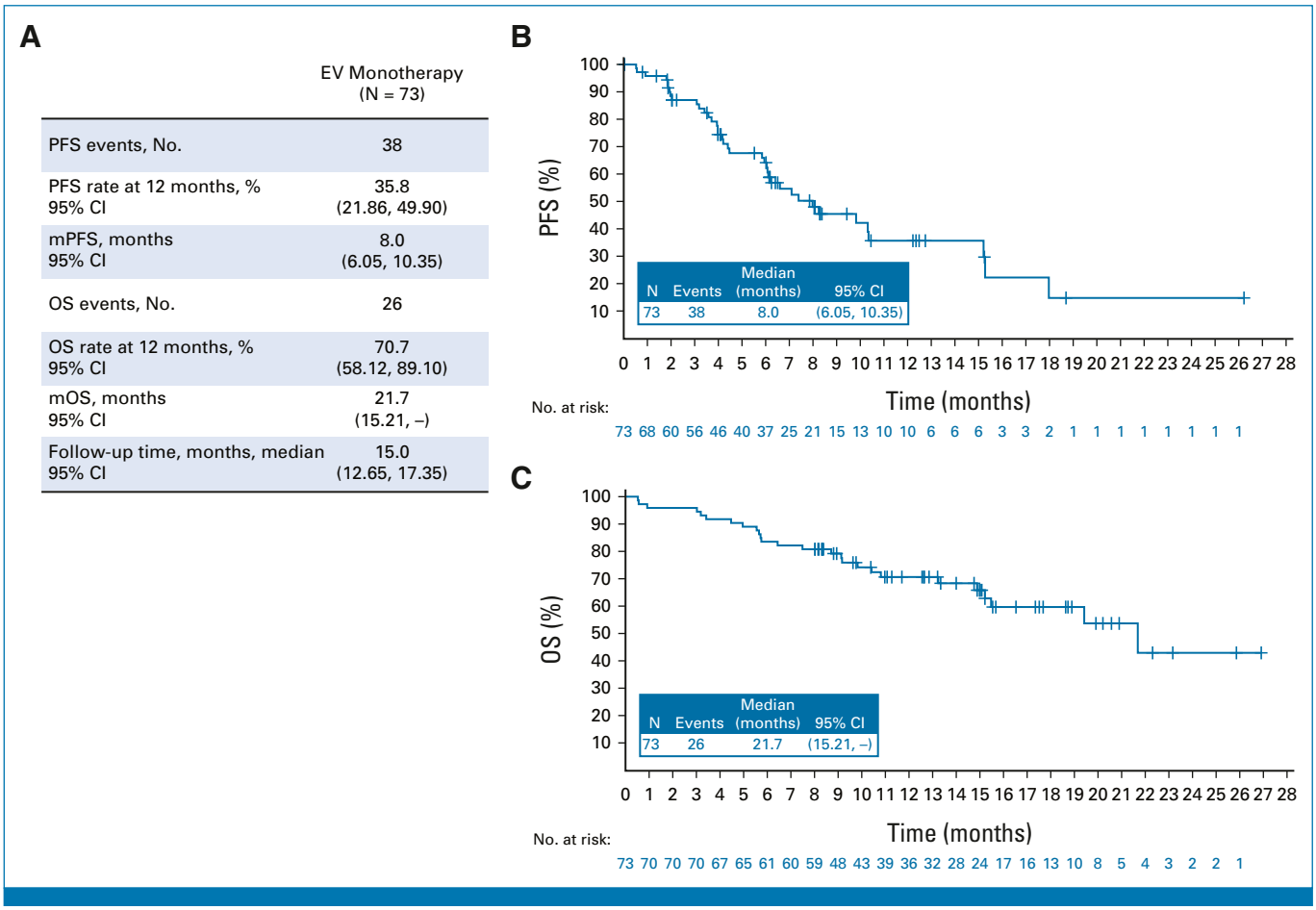

FIG 5. EV monotherapy. (A) PFS per BICR by RECIST v1.1, OS, and median follow-up time. (B) Kaplan-Meier estimates of PFS per BICR by RECIST v1.1. (C) Kaplan-Meier estimates of OS. Preliminary mPFS and mOS are reported here and are expected to evolve over time. At the time of data cutoff, 46 (of 73) patients remain on study for OS follow-up. BICR, blinded independent central review; EV, enfortumab vedotin; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; v1.1, version 1.1.

median DOR has not yet been reached for the combination arm. These results stand out from historical data for gemcitabine and carboplatin chemotherapy and confirm the findings of EV-103 Dose Escalation/Cohort A. These data suggest that the EV plus Pembro combination represents a potential new therapeutic option as a 1L regimen for cisplatin-ineligible patients with la/mUC.

Pembro is an US Food and Drug Administration–approved option that has shown durable responses as monotherapy but is currently restricted in the 1L setting to platinum-ineligible patients.[16,19,31] Avelumab maintenance therapy has shown a survival benefit compared with observation after platinum-based chemotherapy, but it is only an option for patients who remain free from disease progression after four to six cycles of 1L platinum-based therapy. In fact, modeling data suggest that approximately half of patients with la/mUC may not be eligible for maintenance therapy.[14] Despite the availability of these therapies, approximately 60% of cisplatin-ineligible patients with la/mUC who receive 1L treatment never receive 2L treatment, likely because of early progression, tolerability, or short DORs.[20] At the time of the primary analysis, the minority of patients in this study had data captured on subsequent therapies; thus this study required additional follow-up to determine whether there is any potential effect from subsequent treatments on patient outcomes.

A high unmet need remains for a highly efficacious 1L treatment option with rapid and durable responses and a manageable safety profile so that a larger proportion of the cisplatin-ineligible population with la/mUC receives more durable therapeutic benefit. In this study, the overall response rates reported for patients in Cohort K (from either arm) numerically exceeded those reported in trials for the current standard for cisplatin-ineligible patients, gemcitabine plus carboplatin, or for PD-1/PD-L1 CPIs as monotherapies.[16,17,19,32,33]

Although the primary objective was to evaluate the efficacy and safety of the combination, the monotherapy arm was studied to characterize the activity of EV alone in this patient population. The overall response rate of patients treated with EV in the monotherapy arm was 45.2%. The monotherapy

TABLE 2. TRAEs

Variable	EV + Pembro (N = 76) No. (%)	EV Monotherapy (N = 73) No. (%)
Grade ≥3 TRAEs	48 (63.2)	35 (47.9)
Serious TRAEs	18 (23.7)	11 (15.1)
TRAEs leading to death	3 (3.9)	2 (2.7)
TRAEs leading to discontinuation of EV only[a]	19 (25.0)	14 (19.2)
TRAEs leading to discontinuation of pembro only[a]	17 (22.4)	NA
TRAEs leading to discontinuation of either EV or pembro	36 (47.4)	14 (19.2)
TRAEs leading to discontinuation of both EV and pembro[a]	4 (5.3)	NA

TRAEs Occurring in ≥20% All Grade or ≥5% Grade ≥3 (preferred term)[b]	Any Grade No. (%)	Grade ≥3 No. (%)	Any Grade No. (%)	Grade ≥3 No. (%)
Fatigue	43 (56.6)	7 (9.2)	29 (39.7)	6 (8.2)
Peripheral sensory neuropathy	39 (51.3)	1 (1.3)	32 (43.8)	2 (2.7)
Alopecia	35 (46.1)	0	26 (35.6)	0
Rash maculopapular	35 (46.1)	13 (17.1)	21 (28.8)	1 (1.4)
Pruritus	30 (39.5)	3 (3.9)	19 (26.0)	1 (1.4)
Dysgeusia	23 (30.3)	0	25 (34.2)	0
Weight decreased	23 (30.3)	3 (3.9)	21 (28.8)	1 (1.4)
Diarrhea	22 (28.9)	5 (6.6)	20 (27.4)	4 (5.5)
Decreased appetite	20 (26.3)	0	28 (38.4)	0
Nausea	19 (25.0)	0	25 (34.2)	1 (1.4)
Anemia	14 (18.4)	5 (6.6)	11 (15.1)	4 (5.5)
Alanine aminotransferase increased	7 (9.2)	4 (5.3)	0	0
Hyperglycemia	10 (13.2)	5 (6.6)	8 (11.0)	7 (9.6)
Lipase increased	6 (7.9)	5 (6.6)	1 (1.4)	0
Neutropenia	9 (11.8)	7 (9.2)	5 (6.8)	5 (6.8)
Hypophosphatemia	7 (9.2)	4 (5.3)	5 (6.8)	4 (5.5)
Pneumonitis	7 (9.2)	4 (5.3)	3 (4.1)	0

Abbreviations: EV, enfortumab vedotin; NA, not available; Pembro, pembrolizumab; TRAE, treatment-related adverse event.
[a]TRAEs leading to discontinuation of EV, pembro, or both, are not mutually exclusive. A patient can be counted in multiple categories.
[b]TRAEs occurring in ≥20% (any grade) and ≥5% (grade 3 or higher) of patients.

arm demonstrated a manageable safety profile, consistent with previous EV monotherapy studies.[22,26,34]

The ORRs observed in this study were consistent across a range of prespecified subgroups, including patients with liver metastases, and antitumor activity was seen regardless of PD-L1 status. High nectin-4 expression was observed, and the median and distribution was similar between responders and nonresponders. The preliminary PFS and OS results reported here are promising, and data will evolve with additional follow-up, which are trending similarly to median OS found in previously disclosed Dose Escalation/Cohort A data. The safety profile of the combination was manageable and consistent with results from Cohort A of EV-103, with no new safety concerns emerging.[26,35]

Most skin reactions and peripheral neuropathy events were grade ≤ 2 in severity, consistent with observations in the previously reported results for EV-103 Dose Escalation/Cohort A. Skin reactions (including the Pembro AEOSI category of severe skin reactions) and pneumonitis are an identified part of the safety profile for both EV and Pembro monotherapy and were more frequently observed in the combination arm. Higher rates of skin reactions were managed with EV treatment interruption, dose reduction, treatment discontinuation (EV and/or Pembro), and/or corticosteroids, as previously described.[36,37] The safety results highlight the importance of educating both health care practitioners and patients; early intervention for AEs are key components of successfully treating patients with the combination.

It is important to note that this study was not designed to make statistical comparisons between arms. Similarly, although the cORR found in the EV + Pembro cohort is numerically higher than contemporary studies, including even cisplatin-based chemotherapy arms, the study was not designed as a direct comparison with current standard-of-care regimens. This

study builds on the promising results from Dose Escalation/Cohort A and further justifies the ongoing investigation of EV with Pembro in a randomized, phase III study compared with cisplatin or carboplatin plus gemcitabine in biomarker-unselected 1L patients (EV-302/KN-A39, ClinicalTrials.gov identifier: NCT04223856). EV + Pembro are also being evaluated in muscle invasive bladder cancer in randomized phase III trials (EV-303/KN-905, ClinicalTrials.gov identifier: NCT03924895 and EV-304/KNK-B15, ClinicalTrials.gov identifier: NCT04700124).

In conclusion, in the 1L cisplatin-ineligible la/mUC patient population with high unmet need, EV + Pembro had a manageable safety profile and resulted in a high ORR with durable responses and encouraging PFS and OS results, which will evolve with follow-up. These results from Cohort K add to the previously reported results from Dose Escalation/Cohort A of this study and indicate that this combination may represent a new 1L treatment option for a patient population with high unmet need.

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DATA SHARING STATEMENT

Deidentified patient-level trial data that underlie the results reported in this publication will be made available on a case-by-case basis to researchers who provide a methodologically sound proposal. Additional documentation may also be made available. Data availability will begin after approval of the qualified request and end 30 days after receipt of data sets. All requests can be submitted to CTDR@seagen.com and will be reviewed by an internal review committee. Please note that the data sharing policy of this clinical study's sponsor, Seagen Inc, requires all requests for clinical trial data be reviewed to determine the qualification of the specific request. This policy is available at https://www.seagen.com/healthcare-professionals/clinical-data-requests and is aligned with BIO's Principles on Clinical Trial Data Sharing (available at https://www.bio.org/blogs/principles-clinical-trial-data-sharing-reaffirm-commitment).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Enfortumab Vedotin With or Without Pembrolizumab in Cisplatin-Ineligible Patients With Previously Untreated Locally Advanced or Metastatic Urothelial Cancer

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Expert Testimony: Seattle Genetics/Astellas

Anne-Sophie Carret
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Stock and Other Ownership Interests: Seagen
Honoraria: Seagen
Travel, Accommodations, Expenses: Seagen

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Stock and Other Ownership Interests: Merck Sharp & Dohme

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Honoraria: UpToDate, Medscape, Peerview, Research To Practice, Clinical Care Options, Physicans' Education Resource, MJH Life Sciences, EMD Serono, Pfizer
Consulting or Advisory Role: Lilly, Merck, Roche/Genentech, AstraZeneca/MedImmune, Bristol Myers Squibb, Seagen, Bayer, BioClin Therapeutics, QED Therapeutics, Pharmacyclics, GlaxoSmithKline, Janssen Oncology, Astellas Pharma, Boehringer Ingelheim, Pfizer/EMD Serono, Mirati Therapeutics, Immunomedics, Tyra Biosciences, Infinity Pharmaceuticals, Gilead Sciences, Hengrui Pharmaceutical, Alligator Bioscience, Imvax
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Patents, Royalties, Other Intellectual Property: Predictor of platinum sensitivity (Inst)

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Cisplatin-Ineligibility Criteria

Criteria	EV + Pembro (N = 76) No. (%)	EV Monotherapy (N = 73) No. (%)
Patient meeting at least one of the following Galsky criteria	76 (100)	72 (98.6)
CrCL <60 and ≥30 mL/min[a]	48 (63.2)	44 (60.3)
Grade ≥2 hearing loss	11 (14.5)	11 (15.1)
ECOG PS of 2	6 (7.9)	9 (12.3)
CrCL <60 and ≥30 mL/min[a] and grade ≥2 hearing loss	7 (9.2)	7 (9.6)
CrCL <60 and ≥30 mL/min[a] and ECOG PS of 2	4 (5.3)	1 (1.4)
Patient considered cisplatin ineligible by the investigator although not meeting Galsky criteria[b]	0	1 (1.4)

Abbreviations: CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; Pembro, pembrolizumab.
[a]Estimated creatinine clearance per Cockcroft-Gault formula or 24-hour urine collection or modification of diet in renal disease equation.
[b]One patient in the EV monotherapy arm was considered cisplatin-ineligible by the investigator because of age and grade 1 hearing loss.

TABLE A2. EV Treatment-Related AEs of Special Interest

	EV + Pembro (N = 76)			EV Monotherapy (N = 73)		
Adverse Event	Any Grade, No. (%)	Grade ≥3, No. (%)	Time to Onset, Any Grade, Median, Months	Any Grade, No. (%)	Grade ≥3, No. (%)	Time to Onset, Any Grade, Median, Months
Skin reactions	51 (67.1)	16 (21.1)	0.53	33 (45.2)	6 (8.2)	0.95
Rashes	50 (65.8)	15 (19.7)	NA	32 (43.8)	5 (6.8)	NA
Severe cutaneous AEs	14 (18.4)	2 (2.6)	NA	13 (17.8)	3 (4.1)	NA
Peripheral neuropathy	46 (60.5)	2 (2.6)	2.99	40 (54.8)	2 (2.7)	2.48
Ocular disorders	20 (26.3)	0	NA	21 (28.8)	0	NA
Dry eye	19 (25.0)	0	1.64	21 (28.8)	0	2.04
Blurred vision	2 (2.6)	0	6.93	5 (6.8)	0	3.45
Corneal disorders	0	0	NA	4 (5.5)	0	3.48
Hyperglycemia	11 (14.5)	5 (6.6)	0.53	8 (11.0)	7 (9.6)	0.69
Infusion-related reactions	3 (3.9)	0	NA	4 (5.5)	0	NA

NOTE. Treatment relatedness is determined by investigator.
Abbreviations: AE, adverse event; EV, enfortumab vedotin; NA, not available; Pembro, pembrolizumab.

TABLE A3. Pembro AEs of Special Interest

Event[a]	EV + Pembro (N = 76)	
	Any Grade, No. (%)	Grade ≥3, No. (%)
Severe skin reactions[b,c]	21 (27.6)	15 (19.7)
Hypothyroidism	10 (13.2)	0
Pneumonitis[b]	7 (9.2)	4 (5.3)
Adrenal insufficiency[b]	3 (3.9)	0
Colitis[b]	3 (3.9)	1 (1.3)
Hyperthyroidism	3 (3.9)	0
Infusion reactions	3 (3.9)	0
Hepatitis[b]	2 (2.6)	2 (2.6)
Myasthenic syndrome[b]	2 (2.6)	2 (2.6)
Myositis[b]	2 (2.6)	0
Pancreatitis[b]	2 (2.6)	1 (1.3)
Hypophysitis	1 (1.3)	0
Myocarditis[b]	1 (1.3)	0
Nephritis[b]	1 (1.3)	1 (1.3)
Thyroiditis	1 (1.3)	0

Abbreviations: AE, adverse event; EV, enfortumab vedotin; Pembro, pembrolizumab.

[a]Treatment-emergent AEs.

[b]Events associated with systemic steroid use: Patients had AEs of special interest associated with systemic steroid use including severe skin reactions (13 of 21 patients, 61.9%), pneumonitis (six of seven patients, 85.7%), adrenal insufficiency (two of three patients, 66.7%), colitis (two of three patients, 66.7%), hepatitis (two of two patients, 100%), myasthenic syndrome (two of two patients, 100%), myositis (one of two patients, 50%), myocarditis (one of one patients, 100%), nephritis (one of one patients, 100%), and pancreatitis (one of two patients, 50%). Attribution-agnostic management with systemic steroids in patients who were treated with prednisone or prednisone equivalent of ≥20 mg/d are included. Systemic steroids were allowed per protocol for management of AEs and may have been used regardless of a clinically assessed attribution as an immune-mediated AE or a non–immune-mediated AE.

[c]Rash, rash erythematous, rash maculopapular, rash pruritic, rash pustular, pruritus, pruritus generalized, lichen planus, and oral lichen planus under category of severe skin reactions are limited to grade 3 or higher.

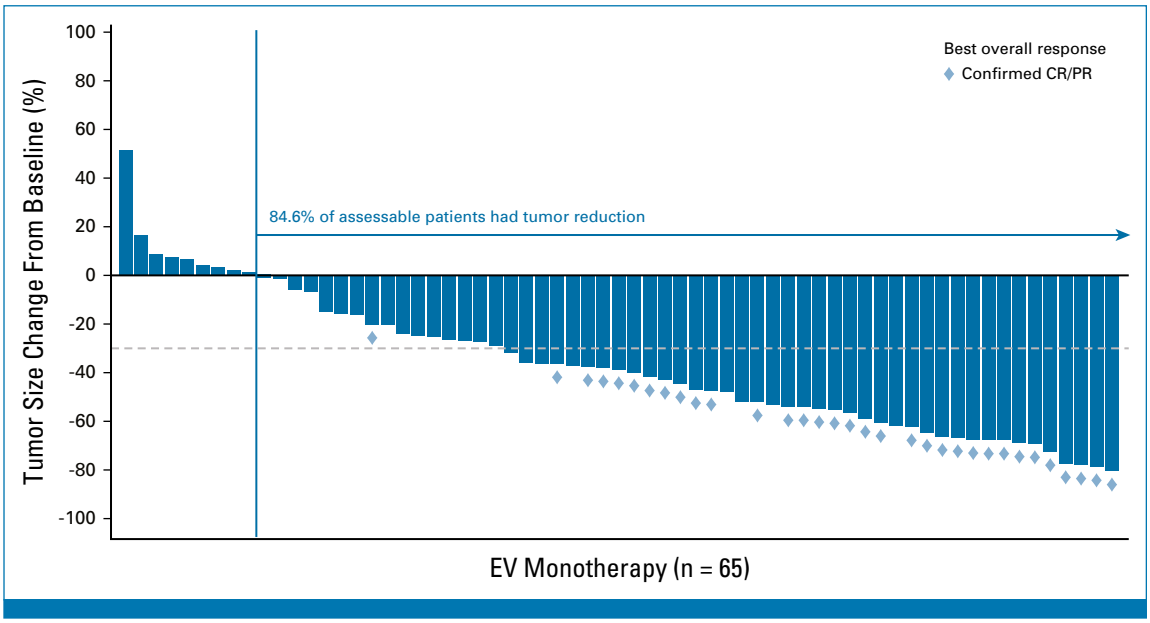

FIG A1. Antitumor activity of EV monotherapy. Waterfall plot of percentage reduction of tumor size from baseline of target lesions by blinded independent central review per RECIST version 1.1. CR, complete response; EV, enfortumab vedotin; PR, partial response.

	EV + Pembro			EV Monotherapy		
Subgroup	**No./N**	**% (95% CI)**	**ORR, % (95% CI)**	**No./N**	**% (95% CI)**	**ORR, % (95% CI)**
Overall	49/76	64.5 (52.7, 75.1)		33/73	45.2 (33.5, 57.3)	
Age, years						
<65	11/17	64.7 (38.3, 85.8)		3/11	27.3 (6.0, 61.0)	
≥65	38/59	64.4 (50.9, 76.4)		30/62	48.4 (35.5, 61.4)	
Sex						
Female	13/22	59.1 (36.4, 79.3)		6/17	35.3 (14.2, 61.7)	
Male	36/54	66.7 (52.5, 78.9)		27/56	48.2 (34.7, 62.0)	
Race						
White	41/61	67.2 (54.0, 78.7)		25/55	45.5 (32.0, 59.4)	
Non-White	8/15	53.3 (26.6, 78.7)		8/18	44.4 (21.5, 69.2)	
ECOG PS						
Grade 0	22/33	66.7 (48.2, 82.0)		13/28	46.4 (27.5, 66.1)	
Grade 1–2	27/43	62.8 (46.7, 77.0)		20/45	44.4 (29.6, 60.0)	
Liver metastasis						
Yes	7/13	53.8 (25.1, 80.8)		7/13	53.8 (25.1, 80.8)	
No	42/63	66.7 (53.7, 78.0)		26/60	43.3 (30.6, 56.8)	
PD-L1 expression						
CPS < 10	27/44	61.4 (45.5, 75.6)		19/38	50.0 (33.4, 66.6)	
CPS ≥ 10	21/31	67.7 (48.6, 83.3)		12/28	42.9 (24.5, 62.8)	
Bajorin risk factors						
0	16/25	64.0 (42.5, 82.0)		8/26	30.8 (14.3, 51.8)	
1	33/51	64.7 (50.1, 77.6)		25/47	53.2 (38.1, 67.9)	
Metastatic disease site at baseline						
Visceral metastases	42/64	65.6 (52.7, 77.1)		28/60	46.7 (33.7, 60.0)	
Lymph nodes only disease	7/10	70.0 (34.8, 93.3)		4/12	33.3 (9.9, 65.1)	
Primary disease site of origin						
Lower tract	31/46	67.4 (52.0, 80.5)		24/52[a]	46.2 (32.2, 60.5)	
Upper tract	18/30	60.0 (40.6, 77.3)		9/21	42.9 (21.8, 66.0)	

FIG A2. Subgroup analysis of ORR in patients treated with EV + Pembro and patients treated with EV monotherapy. [a]One patient had primary disease at both bladder and ureter. CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; ORR, objective response rate; Pembro, pembrolizumab.

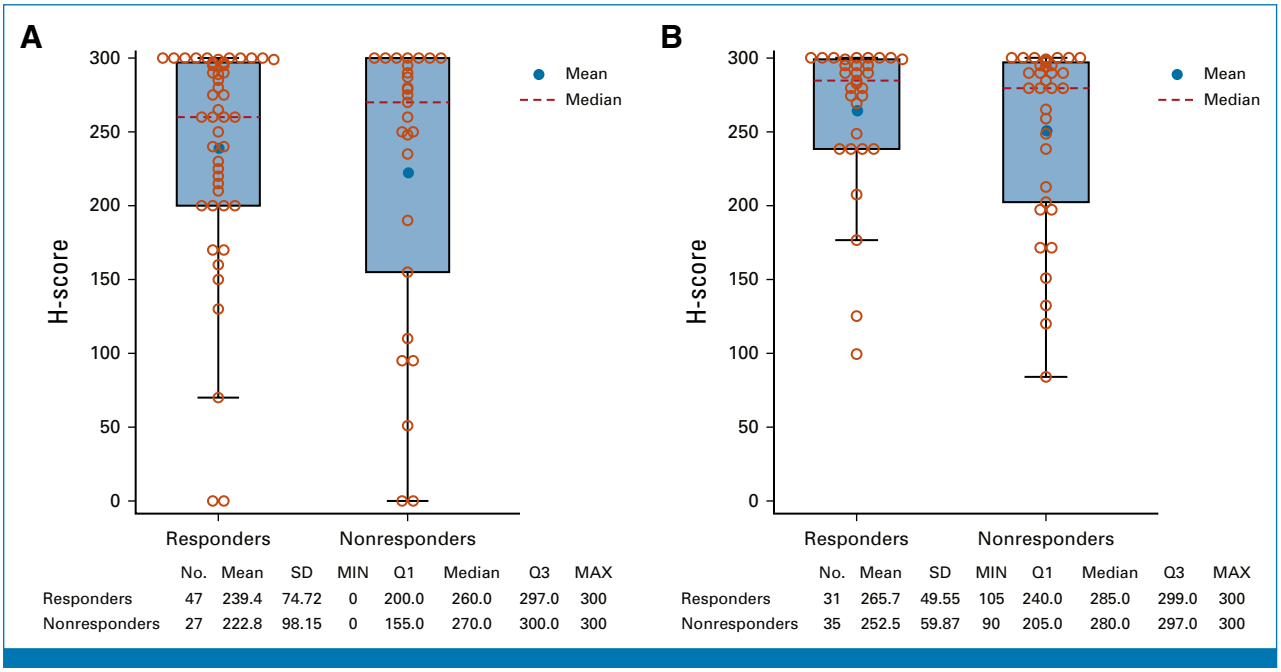

FIG A3. H-score of nectin-4 expression at baseline by best overall response by blinded independent central review in responders and nonresponders. (A) EV + pembrolizumab. (B) EV monotherapy. EV, enfortumab vedotin; MAX, maximum; MIN, minimum; Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation.